Patent claims

1. Process for the parallel preparation of at least 4n oligonucleotides, with the steps:

- arrangement of at least four inserts each with n reaction vessels on a plate such that a first insert is at a first station, a second insert is at a second station, a third insert is at a third station and a fourth insert is at a fourth station, each reaction vessel containing an initiator base bound to an inert carrier, or a universal carrier,
- carrying out in parallel of

a) a deblocking operation to remove protective groups simultaneously in all n reaction vessels of the insert at the first station,

b) a first washing operation simultaneously in all n reaction vessels of the insert at the second station,

c) a coupling operation for attaching individual nucleotides in all n reaction vessels of the insert at the third station, and

d) a second washing operation followed by a capping operation for blocking oligonucleotides which have not undergone the desired chain lengthening in the preceding coupling operation followed by a third washing operation followed by an oxidation operation for stabilizing the phosphate foundation matrix of the oligonucleotides, followed by a fourth washing operation simultaneously in all n reaction vessels of the insert at the fourth station, and

- station by station rotation of the inserts through the four stations mentioned or of the stations relative to the inserts and carrying out of the abovementioned operations until the desired oligonucleotides have been formed by coupling of the individual nucleotides to one another.

2. Process according to claim 1, characterized in that at the second station, together with

the first washing operation carried out there, a monitoring operation which provides information on the quality of the deblocking operation carried out at the first station takes place.

3. Process according to claim 2, characterized in that the monitoring operation comprises an on-line measurement of the conductivity of a washing liquid used for the first washing operation.

4. Process according to claim 2, characterized in that the monitoring operation comprises an on-line measurement of the colour intensity, in particular by measurement by means of UV light, of a washing liquid used for the first washing operation.

5. Process according to one of claims 2 to 4, characterized in that the first washing operation is carried out until the monitoring operation shows that the protective groups removed in the preceding deblocking operation have been rinsed out completely.

6. Process according to one of the preceding claims, characterized in that in the coupling operation carried out at the third station, a selected nucleotide base is added to the reaction vessels simultaneously with an activator, preferably tetrazole.

7. Process according to one of the preceding claims, characterized in that in the coupling operation carried out at the third station, a marking group, in particular a base analogue, a dyestuff or a hapten, is added to the reaction vessels.

8. Process according to one of the preceding claims, characterized in that the reaction vessels are constructed as flow-through vessels, and in that the liquids to be fed

to the reaction vessels in the four stations are conveyed into the reactions vessels and out of them by applying a pressure gradient between the reaction vessel inlet and reaction vessel outlet.

9. Process according to one of the preceding claims, characterized in that all the operations are carried out under an inert gas atmosphere, in particular under nitrogen and/or argon.

10. Device for the parallel preparation of at least 4n oligonucleotides, comprising
- a first station (28) for carrying out a deblocking operation,
- a second station (30) for carrying out a first washing operation,
- a third station (32) for carrying out a coupling operation,
- a fourth station (34) for carrying out a second washing operation followed by a capping operation followed by a third washing operation followed by an oxidation operation followed by a fourth washing operation, the first, the second, the third and the fourth station following one another at a distance in the circumferential direction,
- a plate (16), which has at least four inserts (18) each with n reaction vessels (20) such that a first insert (18) is at the first station (28), a second insert (18) is at the second station (30), a third insert (18) is at the third station (32) and a fourth insert (18) is at the fourth station (34), each reaction vessel (20) being constructed as a flow-through vessel with a reaction vessel inlet and a reaction vessel outlet,
- a device for carrying out a relative movement station by station between the plate (16) and the stations (28, 30, 32, 34),
- a liquid feed device (36) assigned directly to the

reaction vessel inlets in each station (28, 30, 32, 34), and

- a drain channel (40) assigned directly to each reaction vessel outlet in each station (28, 30, 32, 34), each reaction vessel inlet being in tight engagement with the associated liquid feed device (36) and each reaction vessel outlet being in tight engagement with the associated drain channel (40) when the inserts (18) are in a station (28, 30, 32, 34), and there being a small axial distance at least between the reaction vessel inlets and the liquid feed device (36) while a relative movement station by station between the plate (16) and the stations (28, 30, 32, 34) takes place.

11. Device according to claim 10, characterized in that there is also a small axial distance between the reaction vessel outlets and the drain channels (40) while a relative movement station by station between the plate (16) and the stations (28, 30, 32, 34) takes place.

12. Device according to claim 10 or 11, characterized in that the plate (16) is a rotary plate and in that all the liquid feed devices (36) are accommodated in or on a valve-carrying panel (12) and all the drain channels (40) are accommodated in a suction panel (14).

13. Device according to claim 12, characterized in that the valve-carrying panel (12) has a flat contact surface (44) to the upper side of the rotary plate (16) and the suction panel (14) has a flat contact surface (48) to the under-side of the rotary plate (16), and in that the reaction vessel inlets are constructed flush with the upper side of the rotary plate (16) and the reaction vessel outlets are constructed flush with the under-side of the rotary plate (16).

14. Device according to one of claims 10 to 13, characterized in that each liquid feed device (36) has n feed valves (38).

15. Device according to one of claims 12 to 14, characterized in that the valve-carrying panel (12) and the suction panel (14) are fixed against rotation, and in that the rotary plate (16) and the suction panel (14) can be lowered relative to the valve-carrying panel (12).

16. Device according to one of claims 10 to 15, characterized in that each insert (18) extends radially in the plate (16) and has at least one row, preferably two rows parallel to one another, of reaction vessels (20).

17. Device according to one of claims 10 to 16, characterized in that the inserts (18) are made of plastic, in particular of polyether ether ketone.

18. Device according to one of claims 10 to 17, characterized in that each insert (18) has on its longitudinal sides a coding groove (90) of different construction or a coding projection (92) which cooperates with a corresponding coding projection (90') or a corresponding coding groove (92') of the rotary plate (16).

19. Device according to claim 18, characterized in that the inserts (18) can be assembled to reaction vessel panels (94) by means of the coding grooves (90) and coding projections (92).

20. Device according to one of claims 10 to 19, characterized in that the reaction vessel outlet (26) and/or the reaction vessel inlet (24) of each reaction vessel (20) has a constriction point (96) which can be closed by a movable ball (98).

21. Device according to claim 20, characterized in that the ball (98) is pushed in the direction of the constriction point (96) by the force of gravity, by the force of a spring or by magnetic force.

22. Device according to one of claims 10 to 12, characterized in that at least the liquid feed device (36) of the third station (32) has
- a plurality of individual feeds (100), each of which is in liquid connection with only one of the various liquids to be added to the reaction vessels (20) at the station and the number of which corresponds to at least the number of different liquids to be added to the reaction vessels (20) at the station,
- a coupling drive (102) for the individual feeds (100), in order to connect each individual feed (100) with a reaction vessel inlet (24) as required, and
- a common carrier (104) for the individual feeds (100) which can be displaced at right angles to the reaction vessel inlets (24).

23. Device according to claim 22, characterized in that the carrier (104) is constructed as a carriage which can be displaced position by position, each reaction vessel inlet (24) representing a position.

24. Device according to claim 22 or 23, characterized in that the coupling drive (102) in a position of the carrier (104) in which individual feeds (100) are in alignment with reaction vessel inlets (24) connects to a reaction vessel inlet (24) only that individual feed (100) which is connected to the liquid precisely required in the reaction vessel (20) in question, and in that, depending on the requirement, the carrier (104) is then displaced optionally several times into another position in which individual feeds (100) are in alignment with reaction vessel inlets (24) and in which in

turn the coupling drive (102) connects to a reaction vessel inlet (24) only that individual feed (100) which is connected to precisely the liquid required in the reaction vessel (20) in question.

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